CLAIMS

1. A heavy chain of a monoclonal antibody having an agonistic activity, which binds to CD40, wherein the heavy chain comprises an upper hinge and a middle hinge derived from a human IgG2, and a constant region with at least one amino acid deleted or substituted, or with at least one amino acid added thereto, said deletion, substitution or addition being capable of increasing or decreasing ADCC and/or CDC.

2. The heavy chain according to claim 1, wherein the constant region is derived from a human IgG.

3. The heavy chain according to claim 2, wherein the human IgG is a human IgG1.

4. The heavy chain according to claim 2, wherein the human IgG is a human IgG2.

5. The heavy chain according to claim 2, wherein the human IgG is a human IgG3.

6. The heavy chain according to claim 2, wherein the human IgG is a human IgG4.

7. The heavy chain according to any one of claims 3 to 5, wherein said substitution of amino acids in the constant region is substitution of proline with serine at position 331 which is indicated by the EU index as in Kabat et al.

8. A monoclonal antibody comprising the heavy chain according to any one of claims 1 to 7.

9. The heavy chain according to any one of claims 1 to 7, wherein the heavy chain comprises a variable region from a heavy chain of a monoclonal antibody produced by the hybridoma KM341-1-19 (Accession No. FERM BP-7759).

10. A monoclonal antibody consisting of the heavy chain according to claim 9 and a light chain comprising a variable region from a light chain of a monoclonal antibody produced by the hybridoma KM341-1-19 (Accession No. FERM BP-7759).

11. The heavy chain according to any one of claims 1 to 7, wherein the heavy chain comprises a variable region of the polypeptide represented by SEQ ID NO: 38.

12. A monoclonal antibody consisting of the heavy chain according to claim 11 and a light chain of a monoclonal antibody, wherein the light chain comprises a variable region of the polypeptide represented by SEQ ID NO: 40.

13. The heavy chain according to claim 1, wherein the heavy chain consists of a remaining portion provided by removing the signal sequence from the polypeptide represented by SEQ ID NO: 132.

14. A monoclonal antibody consisting of the heavy chain according to claim 13 and a light chain of a monoclonal antibody, wherein the light chain consists of a remaining portion provided by removing the signal sequence from the polypeptide represented by SEQ ID NO: 134.

15. The heavy chain according to claim 1, wherein the heavy chain is produced by a host comprising an expression vector having the polynucleotide represented by SEQ ID NO: 131.

16. The monoclonal antibody according to claim 8, wherein the monoclonal antibody is produced by a host comprising an expression vector having the polynucleotide represented by SEQ ID NO: 131 and the polynucleotide represented by SEQ ID NO: 133.

17. The heavy chain according to any one of claims 1 to 7, wherein the heavy chain comprises a variable region from a heavy chain of a monoclonal antibody produced by the hybridoma 2105 (Accession No. FERM BP-8024).

18. A monoclonal antibody consisting of the heavy chain according to claim 17 and a light chain comprising a variable region from a light chain of a monoclonal antibody produced by the hybridoma 2105 (Accession No. FERM BP-8024).

19. The heavy chain according to any one of claims 1 to 7, wherein the heavy chain comprises a variable region of the polypeptide represented by SEQ ID NO: 42.

20. A monoclonal antibody consisting of the heavy chain according to claim 19 and a light chain of a monoclonal antibody, wherein the light chain comprises a variable region of the polypeptide represented by SEQ ID NO: 44.

21. The heavy chain according to claim 1, wherein the heavy chain consists of a remaining portion provided by removing the signal sequence from the polypeptide represented by SEQ ID NO: 136.

22. A monoclonal antibody consisting of the heavy chain according to claim 21 and a light chain of a monoclonal antibody, wherein the light chain consists of a remaining portion

provided by removing the signal sequence from the polypeptide represented by SEQ ID NO: 138.

23. The heavy chain according to claim 1, wherein the heavy chain is produced by a host comprising an expression vector having the polynucleotide represented by SEQ ID NO: 135.

24. The monoclonal antibody according to claim 8, wherein the monoclonal antibody is produced by a host comprising an expression vector having the polynucleotide represented by SEQ ID NO: 135 and the polynucleotide represented by SEQ ID NO: 137.

25. A polynucleotide represented by SEQ ID NO: 131.

26. A polynucleotide represented by SEQ ID NO: 133.

27. An expression vector having the polynucleotide according to claim 25.

28. An expression vector having the polynucleotide according to claim 26.

29. An expression vector having the polynucleotides according to claims 25 and 26.

30. A host comprising the expression vector according to claim 27.

31 A host comprising the expression vector according to claim 28.

32. A host comprising the expression vector according to claim 29.

33. A process of producing a heavy chain of a monoclonal antibody, comprising the steps of: culturing the host according to claim 30 in a culture medium; and obtaining a heavy chain of a monoclonal antibody from the culture and/or the host.

34. A process of producing a monoclonal antibody, comprising the steps of: culturing the host according to claim 32 in a culture medium; and obtaining a monoclonal antibody from the culture and/or the host.

35. A polynucleotide represented by SEQ ID NO: 135.

36. A polynucleotide represented by SEQ ID NO: 137.

37. An expression vector having the polynucleotide according to claim 35.

38. An expression vector having the polynucleotide according to claim 36.

39. An expression vector having the polynucleotides according to claims 35 and 36.

40. A host comprising the expression vector according to claim 37.

41. A host comprising the expression vector according to claim 38.

42. A host comprising the expression vector according to claim 39.

43. A process of producing a heavy chain of a monoclonal antibody, comprising the steps of: culturing the host according to claim 40 in a culture medium; and obtaining a heavy chain of a monoclonal antibody from the culture and/or the host.

44. A process of producing a monoclonal antibody, comprising the steps of: culturing the host according to claim 42 in a culture medium; and obtaining a monoclonal antibody from the culture and/or the host.

45. A process of producing a heavy chain of a monoclonal antibody having an agonistic activity capable of binding to CD40, comprising the step of substituting the upper hinge and the middle hinge of an antibody, which is not either an upper hinge or a middle hinge derived from a human IgG2, with an upper hinge and a middle hinge derived from a human IgG2, respectively.

46. A process of producing a heavy chain of a monoclonal antibody comprising a variable region, and an upper hinge and a middle hinge derived from a human IgG2, comprising the step of identifying a polypeptide forming the variable region, which is from a heavy chain of a monoclonal antibody capable of binding to CD40.

47. A process of producing a monoclonal antibody having an agonistic activity capable of binding to CD40, comprising the step of substituting the upper hinge and the middle hinge of an antibody, which is not either an upper hinge or a middle hinge derived from a human IgG2, with an upper hinge and a middle hinge derived from a human IgG2, respectively.

48. A process of producing a monoclonal antibody comprising a variable region, and an upper hinge and a middle hinge derived from a human IgG2, comprising the step of identifying a polypeptide forming the variable region, which is from a heavy chain of a monoclonal antibody capable of binding to CD40.

49. A pharmaceutical composition comprising the monoclonal antibody according to any one of claims 8, 10, 12, 14, 16, 18, 20, 22 and 24 as an active ingredient.

50. The pharmaceutical composition according to claim 49 used for prevention or treatment of a malignant tumor, a pathogen or an autoimmune disease.

51. A method of prevention or treatment of a malignant tumor, a pathogen or an autoimmune disease, comprising administration of the pharmaceutical composition according to claim 49 into a mammal.

52 Use of the monoclonal antibody according to any one of claims 8, 10, 12, 14, 16, 18, 20, 22 and 24 for production of a pharmaceutical composition used for prevention or treatment of a malignant tumor, a pathogen or an autoimmune disease.

53. A heavy chain of a monoclonal antibody having an antagonistic activity capable of binding to CD40, wherein the heavy chain comprises a constant region with at least one amino acid deleted or substituted, or with at least one amino acid added thereto, said deletion, substitution or addition being capable of increasing or decreasing ADCC and/or CDC.

54. The heavy chain according to claim 53, wherein the constant region is derived from a human IgG.

55. The heavy chain according to claim 54, wherein the human IgG is a human IgG1.

56. The heavy chain according to claim 54, wherein the human IgG is a human IgG2.

57. The heavy chain according to claim 54, wherein the human IgG is a human IgG3.

58. The heavy chain according to claim 54, wherein the human IgG is a human IgG4.

59. The heavy chain according to any one of claims 55, 57 and 58, wherein said substitution of amino acids in the constant region is substitution of leucine with glutamic acid at position 235 which is indicated by the EU index as in Kabat et al.

60. A heavy chain according to any one of claims 53 to 59, wherein the heavy chain comprises a constant region with at least one amino acid deleted or substituted, or with at least one amino acid added thereto, said deletion, substitution or addition being capable of promoting the formation of the S-S bond between the heavy chains.

61. The antibody heavy chain according to claim 60, wherein said substitution of amino acids in the constant region is substitution of serine with proline at position 228 which is indicated by the EU index as in Kabat et al.

62. A monoclonal antibody comprising the heavy chain according to any one of claims 53 to 61.

63. The heavy chain according to any one of claims 53 to 61, wherein the heavy chain comprises a variable region from a heavy chain of a monoclonal antibody produced by the hybridoma 4D11 (Accession No. FERM BP-7758).

64. A monoclonal antibody consisting of the heavy chain according to claim 63 and a light chain comprising a variable region from a light chain of a monoclonal antibody produced by the hybridoma 4D11 (Accession No. FERM BP-7758).

65. The heavy chain according to any one of claims 53 to 61, wherein the heavy chain comprises a variable region of the polypeptide represented by SEQ ID NO: 46.

66. A monoclonal antibody consisting of the heavy chain according to claim 65 and a light chain of a monoclonal antibody, wherein the light chain comprises a variable region of the polypeptide represented by SEQ ID NO: 48.

67. The heavy chain according to claim 53, wherein the heavy chain consists of a remaining portion provided by removing the signal sequence from the polypeptide represented by SEQ ID NO: 140.

68. A monoclonal antibody consisting of the heavy chain according to claim 67 and a light chain of a monoclonal antibody, wherein the light chain consists of a remaining portion provided by removing the signal sequence from the polypeptide represented by SEQ ID NO: 142.

69. The heavy chain according to claim 53, wherein the heavy chain is produced by a host comprising an expression vector having the polynucleotide represented by SEQ ID NO: 139.

70. The monoclonal antibody according to claim 62, wherein the monoclonal antibody is produced by a host comprising an expression vector having the polynucleotide represented by SEQ ID NO: 139 and the polynucleotide represented by SEQ ID NO: 141.

71. A polynucleotide represented by SEQ ID NO: 139.

72. A polynucleotide represented by SEQ ID NO: 141.

73. An expression vector having the polynucleotide according to claim 71.

74. An expression vector having the polynucleotide according to claim 72.

75. An expression vector having the polynucleotides according to claims 71 and 72.

76. A host comprising the expression vector according to claim 73.

77. A host comprising the expression vector according to claim 74.

78. A host comprising the expression vector according to claim 75.

79. A process of producing a heavy chain of a monoclonal antibody, comprising the steps of: culturing the host according to claim 76 in a culture medium; and obtaining a heavy chain of a monoclonal antibody from the culture and/or the host.

80. A process of producing a monoclonal antibody, comprising the steps of: culturing the host according to claim 78 in a culture medium; and obtaining a monoclonal antibody from the culture and/or the host.

81. A pharmaceutical composition comprising the monoclonal antibody according to any one of claims 62, 64, 66, 68 and 70 as an active ingredient.

82. The pharmaceutical composition according to claim 81 used for prevention or treatment of transplant rejection, autoimmune diseases, allergy or blood clotting factor VIII inhibition.

83. A method of prevention or treatment of transplant rejection, autoimmune diseases, allergy or blood clotting factor VIII inhibition, which comprises administering the pharmaceutical composition according to claim 81 into a mammal.

84. Use of the monoclonal antibody according to any one of claims 62, 64, 66, 68 and 70 for production of a pharmaceutical composition used for prevention or treatment of transplant rejection, autoimmune diseases, allergy or blood clotting factor VIII inhibition.

85. A method of producing a heavy chain of a monoclonal antibody having an antagonistic activity capable of binding to CD40, wherein the agonistic activity is lowered, comprising the step of carrying out deletion or substitution of at least one amino acid, or addition of at least one amino acid in the heavy chain constant region of a human antibody.

86. The method according to claim 85, wherein the constant region is derived from a human IgG.

87. The method according to claim 86, wherein the human IgG is a human IgG4.

88. The method according to any one of claims 85 to 87, wherein said substitution of amino acids in the constant region is substitution of leucine with glutamic acid at position 235 which is indicated by the EU index as in Kabat et al.

89. A polynucleotide provided by removing the portion encoding the signal sequence from the polynucleotide represented by SEQ ID NO: 131.

90. A polynucleotide provided by removing the portion encoding the signal sequence from the polynucleotide represented by SEQ ID NO: 133.

91. A polynucleotide provided by removing the portion encoding the signal sequence from the polynucleotide represented by SEQ ID NO: 135.

92. A polynucleotide provided by removing the portion encoding the signal sequence from the polynucleotide represented by SEQ ID NO: 137.

93. A polynucleotide provided by removing the portion encoding the signal sequence from the polynucleotide represented by SEQ ID NO: 139.

94. A polynucleotide provided by removing the portion encoding the signal sequence from the polynucleotide represented by SEQ ID NO: 141.